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5/15/06 KR

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ile 155:MEDLINE(R) 1951-2006/May 18
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      Set  Items  Description
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Cost is in DialUnits
? ds
Terminal set to DLINK
? s mutant? or mutation? or mutagenesis? or alter? or alteration? or deletion?
or substitu? or addition? or insertion?

Set     Items   Description
S1        778   CHOLERA? (25N) ADJUVANT?
S2         90   S1 AND (PORTION? OR FRAGMENT? OR MINIMAL?)
S3         45   S1 (25N) (PORTION? OR FRAGMENT? OR MINIMAL?)
S4         32   S3 AND (DOMAIN? OR SUBUNIT? OR ALPHA?)
S5          6   S2 AND MOIET?
S6         34   S4 OR S5
S7     253530   (A OR ALPHA) (5N) (DOMAIN? OR MOIET? OR FRAGMENT? OR PORTI-
             ON? OR SUBUNIT?)
S8        780   S7 (10N) CHOLERA?
S9        177   S8 AND (ADJUVANT? OR ENHANC?)
S10        14   S9 AND HOLOTOXIN?
? s cholera? or (ct(n)a1) or cta or cta1 or holotoxin?
          223900  MUTANT?
          356134  MUTATION?
           86249  MUTAGENESIS?
          709495  ALTER?
          209703  ALTERATION?
          115810  DELETION?
          177531  SUBSTITU?
          952456  ADDITION?
           78846  INSERTION?
     S11 2095629  MUTANT? OR MUTATION? OR MUTAGENESIS? OR ALTER? OR
                  ALTERATION? OR DELETION? OR SUBSTITU? OR ADDITION? OR
                  INSERTION?
?
           22028  CHOLERA?
          121609  CT
           21506  A1
               8  CT(N)A1
            1856  CTA
              69  CTA1
             379  HOLOTOXIN?
     S12   24155  CHOLERA? OR (CT(N)A1) OR CTA OR CTA1 OR HOLOTOXIN?
?
? s s11 and s12
         2095629  S11
           24155  S12
     S13    5562  S11 AND S12
? s s11 (25n) s12
         2095629  S11
           24155  S12
     S14    2627  S11 (25N) S12
? s s14 and adjuvant?
            2627  S14
           86652  ADJUVANT?
     S15     140  S14 AND ADJUVANT?
? s s1 and s15
             778  S1
             140  S15
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     S16      116  S1 AND S15
? s s16 and (alpha (5n) subunit?)
             116  S16
          555089  ALPHA
          156562  SUBUNIT?
           36490  ALPHA(5N)SUBUNIT?
     S17       0  S16 AND (ALPHA (5N) SUBUNIT?)
? s16/kwic/all
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16/KWIC/73

We exploited the powerful **adjuvant** properties of **cholera holotoxin** (CT) to create a mucosally administered subunit vaccine against respiratory syncytial virus (RSV). A genetically detoxified **mutant** CT with an E to H **substitution** at amino acid 29 of the **CT - A1** subunit (CT-E29H) was compared to wild type CT for toxicity and potential use as an intranasal (IN) **adjuvant** for the natural fusion (F) protein of RSV. When compared to CT the results demonstrated...

... vaccinated with 0.01 microg CT-E29H or IM with F protein adsorbed to AlOH **adjuvant** . In addition, the formulation of purified F protein and CT-E29H (0.1 and 1...

... RSV challenge. Collectively, the data have important implications for vaccine strategies that use genetically detoxified **mutant cholera holotoxins** for the mucosal delivery of highly purified RSV antigens.

16/KWIC/67
DIALOG(R)File 155:(c) format only 2006 Dialog. All rts. reserv.

Cutting edge: the mucosal adjuvant cholera **toxin redirects vaccine proteins into olfactory tissues.**

We tested the notion that the mucosal **adjuvant cholera** toxin (CT) could target, in **addition** to nasal-associated lymphoreticular tissues, the olfactory nerves/epithelium (ON/E) and olfactory bulbs (OBs...

... monosialoganglioside (GM1) dependent. Intranasal vaccination with (125)I-tetanus toxoid together with unlabeled CT as **adjuvant** resulted in uptake into the ON/E but not the OB, whereas (125)I-tetanus...

Descriptors: ***Adjuvants** , Immunologic--administration and dosage--AD; *Axonal Transport--immunology--IM; * **Cholera** Toxin--administration and dosage--AD; * **Cholera** Vaccines--administration and dosage--AD; *Nasal Mucosa--immunology--IM; *Nasal Mucosa--innervation--IR; **Adjuvants** , Immunologic--pharmacokinetics--PK; Administration, Intranasal; Animals; Brain--immunology--IM; Brain--metabolism--ME; **Cholera** Toxin--immunology --IM; **Cholera** Toxin--pharmacokinetics--PK; **Cholera** Vaccines --immunology--IM; **Cholera** Vaccines--pharmacokinetics--PK; G(M1) Ganglioside--physiology--PH; Iodine Radioisotopes--pharmacokinetics--PK; Mice; Mice, Inbred...

Chemical Name: **Adjuvants** , Immunologic; **Cholera** Vaccines; Io

16/KWIC/66
DIALOG(R)File 155:(c) format only 2006 Dialog. All rts. reserv.

... formalin-killed bacteria and cholera toxin B subunit, protects the vaccinees (>5 years old) from **cholera** for 6 months. Vietnamese WC, a heat- and formalin-killed vaccine, is inexpensive and effective even for 1 to 5-year-old children. **Additionally** , irradiated WC vaccines and new serotype (O139) vaccines are being developed. Regarding intestinal immunity, secretory IgA has been mainly examined. In **addition** , mucosal IgG, as induced by the irradiated WC vaccine, should also be investigated. Development of mucosal **adjuvant** , such as **holotoxin** -type **mutants** of **cholera** toxin and related Escherichia coli heat-labile enterotoxin, has been actively undertaken. Diverse custom-made...

16/KWIC/39
DIALOG(R)File 155:(c) format only 2006 Dialog. All rts. reserv.

· **Detoxification of** cholera **toxin without removal of its immunoadjuvanticity by the** addition **of (STa-related) peptides to the catalytic subunit. A potential new strategy to generate immunostimulants...**
...heat-stable enterotoxin STa were fused to the N terminus of the A-subunit of **cholera** toxin (**CTA**) to explore whether peptide **additions** could help generate detoxified **cholera** toxin (CT) derivatives. Proteins carrying APRPGP (6- **CTA**), ASRCAELCCNPACPAP (16- **CTA**), or ANSSNYCCELCCNPACTGCYPGP (23- **CTA**) were genetically constructed. Using a two-plasmid system these derivatives were co-expressed in Vibrio...

... immune responses to a co-administered heterologous protein antigen, although in variable degrees. Therefore, the **addition** of STa-related peptides to **CTA** reduced the toxicity of CT while partly preserving its natural immunoadjuvanticity. These results suggest peptide extensions to **CTA** are a useful **alternative** to site-directed **mutagenesis** to detoxify CT. The simplicity of the procedure, combined with efficient expression and assembly of...
; Adenosine Diphosphate Ribose--metabolism--ME; **Adjuvants** , Immunologic --pharmacology--PD; Amino Acid Sequence; Animals; Blotting, Western; Catalytic Domain; Cyclic AMP--metabolism--ME...
Chemical Name: **Adjuvants** , Immunologic; DNA, Complementary; Peptides; Plasmids; Recombinant Fusion Proteins; Adenosine Diphosp

13249360 PMID: 11395467

Biological and biochemical characterization of variant A subunits **of** cholera **toxin constructed by site-directed mutagenesis.**

Jobling M G; Holmes R K

Department of Microbiology, University of Colorado Health Sciences Center, Denver, Colorado 80220, USA.

Journal of bacteriology (United States) Jul 2001, 183 (13) p4024-32, ISSN 0021-9193--Print Journal Code: 2985120R

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Cholera toxin (CT) is the prototype for the Vibrio cholerae-Escherichia coli family of heat-labile enterotoxins having an AB5 structure. By substituting amino acids in the enzymatic A subunit that are highly conserved in all members of this family, we constructed 23 variants of CT that exhibited decreased or undetectable toxicity and we characterized their biological and biochemical properties. Many variants exhibited previously undescribed temperature-sensitive assembly of **holotoxin** and/or increased sensitivity to proteolysis, which in all cases correlated with exposure of epitopes of CT-A that are normally hidden in native CT **holotoxin** . Substitutions within and deletion of the entire active-site-occluding loop demonstrated a prominent role for His-44 and this loop in the structure and activity of CT. Several novel variants with wild-type assembly and stability showed significantly decreased toxicity and enzymatic activity (e.g., variants at positions R11, I16, R25, E29, and S68+V72). In most variants the reduction in toxicity was proportional to the decrease in enzymatic activity. For substitutions or insertions at E29 and Y30 the decrease in toxicity was 10- and 5-fold more than the reduction in enzymatic activity, but for variants with R25G, E110D, or E112D substitutions the decrease in enzymatic activity was 12- to 50-fold more than the reduction in toxicity. These variants may be useful as tools for additional studies on the cell biology of toxin action and/or as attenuated toxins for **adjuvant** or vaccine use.

Descriptors: *Cholera Toxin--genetics--GE; *Cholera Toxin--toxicity--TO; *Escherichia coli Proteins; ADP-Ribosylation Factors--genetics--GE; ADP-Ribosylation Factors--immunology--IM; ADP-Ribosylation Factors --toxicity--TO; Amino Acid Sequence; Bacterial Toxins--genetics--GE; Bacterial Toxins--toxicity--TO; Binding Sites; Cholera Toxin--immunology --IM; Comparative Study; Conserved Sequence; Enterotoxins--genetics--GE; Enterotoxins--toxicity--TO; Enzyme Stability; Epitopes; Models, Molecular; Mutagenesis, Site-Directed; Protein Conformation; Re

16/KWIC/79

Mutants **of** cholera **toxin as an effective and safe** adjuvant **for nasal influenza vaccine.**

The effectiveness and safety of **mutants** of **cholera** toxin (CT) as an **adjuvant** for nasal influenza vaccine was examined. Four CT **mutants**, called CT7 K (Arg to Lys), CT61F (Arg to Phe), CT112 K (Glu to Lys...

... CTB IgE Ab responses were induced. The mutant CT112 K, which showed a relatively high **adjuvant** activity, the lowest toxicity and relatively high yields in a bacterial culture, seems to be the most effective and safest **adjuvant** for nasal influenza vaccine among those examined. The low dose of CT derivatives or vaccine...

... tentative plan for safety standards for human use of CT (or LT) derivatives as an **adjuvant** of nasal influenza vaccine is discussed.

Descriptors: ***Adjuvants**, Immunologic--genetics--GE; * **Cholera** Toxin --immunology--IM; *Influenza Vaccines--immunology--IM; * **Mutation** --immunology--IM; *Orthomyxoviridae Infections--prevention and control--PC; *Vaccines, Synthetic--immunology--IM; **Adjuvants**, Immunologic--adverse effects--AE; Administration, Intranasal; Animals; Antibodies, Viral --biosynthesis--BI; **Cholera** Toxin--genetics--GE; Drug Stability; Immunity, Mucosal; Immunoglobulin E--biosynthesis--BI; Influenza Vaccines --adverse effects--AE; Influenza Vaccines--genetics--GE; Mice; Mice, Inbred BALB C; **Mutagenesis**, Site-Directed; Vaccines, Synthetic--genetics --GE

Chemical Name: **Adjuvants**, Immunologic; Antibodies, Viral; Influenza Vaccines; Vaccines, Synthetic; Immunoglobulin E; **Cholera** Toxin

16/KWIC/90
DIALOG(R)File 155:(c) format only 2006 Dialog. All rts. reserv.

A nontoxic adjuvant **for mucosal immunity to pneumococcal surface protein A.**

... we demonstrated that pneumococcal surface protein A (PspA) nasally administered with a nontoxic A subunit **mutant** of **cholera** toxin (mCT) S61F elicited a protective immune response. Immunization with PspA and mCT elicited higher...

... and nasal secretions. These responses were dependent on the use of mCT as a mucosal **adjuvant** . The PspA-specific Ab responses induced by mCT S61F were comparable with those induced by...

; **Adjuvants** , Immunologic--administration and dosage--AD; Administration, Intranasal; Animals; Antigens, Bacterial--administration and dosage--AD; Antigens, Bacterial--immunology--IM; Bacterial Proteins --administration and dosage--AD; Bacterial Vaccines--administration and dosage--AD; **Cholera** Toxin--administration and dosage--AD; **Cholera** Toxin--genetics--GE; Mice; Mice, Inbred C57BL; **Mutation** ; Pneumococcal Infections--prevention and control--PC; Research Support, Non-U.S. Gov't; Research Support...

Chemical Name: **Adjuvants** , Immunologic; Antigens, Bacterial; Bacterial Proteins; Bacterial Vaccines; pneumococcal surface protein A; **Cholera** Toxin

WEST Search History

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DATE: Monday, May 15, 2006

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☐	L1	20040176571	1
	DB=PGPB,USPT,USOC,EPAB,JPAB,DWPI,TDBD; PLUR=YES; OP=OR		
☐	L2	(cholera or subunit or sub-unit) same 29	4288
☐	L3	(cholera or subunit or sub-unit) near25 29	980
☐	L4	l3 same alpha$	164
☐	L5	l4 and (vibrio or cholera)	46
☐	L6	l1 and l2	1
☐	L7	l1 and l3	1
☐	L8	l1 and l4	0

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DATE: Monday, May 15, 2006

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	DB=PGPB; PLUR=YES; OP=OR		
☐	L1	20040176571	1
	DB=PGPB,USPT,USOC,EPAB,JPAB,DWPI,TDBD; PLUR=YES; OP=OR		
☐	L2	(cholera or subunit or sub-unit) same 29	4288
☐	L3	(cholera or subunit or sub-unit) near25 29	980
☐	L4	l3 same alpha$	164
☐	L5	l4 and (vibrio or cholera)	46

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L5: Entry 2 of 46 File: PGPB Jan 19, 2006

DOCUMENT-IDENTIFIER: US 20060014926 A1
TITLE: Human papillomavirus polypeptides and immunogenic compositions

Description of Disclosure:
[0103] Other adjuvants include mineral oil and water emulsions, aluminum salts (alum), such as aluminum hydroxide, aluminum phosphate, etc., Amphigen, Avridine, L121/squalene, D-lactide-polylactide/glycoside, muramyl dipeptide, killed Bordetella, saponins, such as Quil A or Stimulon.TM. QS-21 (Antigenics, Framingham, Mass.), described in U.S. Pat. No. 5,057,540, which is hereby incorporated by reference, and particles generated therefrom such as ISCOMS (immunostimulating complexes). Mycobacterium tuberculosis, bacterial lipopolysaccharides, synthetic polynucleotides such as oligonucleotides containing a CpG motif (U.S. Pat. No. 6,207,646, which is hereby incorporated by reference), cholera toxin (either in a wild-type or mutant form, e.g., wherein the glutamic acid at amino acid position 29 is replaced by another amino acid, preferably a histidine, in accordance with International Patent Publication No. WO 00/18434, incorporated herein by reference), a pertussis toxin (PI), or an E. coli heat-labile toxin (LT), particularly LT-K63, LT-R72, CT-S109, PT-K9/G129; see, e.g., International Patent Publication Nos. WO 93/13302 and WO 92/19265, incorporated herein by reference. Various cytokines and lymphokines are suitable for use as adjuvants. One such adjuvant is granulocyte-macrophage colony stimulating factor (GM-CSF), which has a nucleotide sequence as described in U.S. Pat. No. 5,078,996, which is hereby incorporated by reference. A plasmid containing GM-CSF cDNA has been transformed into E. coli and has been deposited with the American Type Culture Collection (ATCC), 10801 University Boulevard, Manassas, Va. 20110-2209, under Accession Number 39900. The cytokine Interleukin-12 (IL-12) is another adjuvant that is described in U.S. Pat. No. 5,723,127, which is hereby incorporated by reference. Other cytokines or lymphokines have been shown to have immune modulating activity, including, but not limited to, the interleukins 1-alpha, 1-beta, 2, 4, 5, 6, 7, 8, 10, 13, 14, 15, 16, 17 and 18, the interferons-alpha, beta and gamma, granulocyte colony stimulating factor, and the tumor necrosis factors alpha and beta, and are suitable for use as adjuvants.

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L5: Entry 5 of 46 File: PGPB Nov 10, 2005

DOCUMENT-IDENTIFIER: US 20050249746 A1
TITLE: Mutants of the p4 protein of nontypable haemophilus influenzae with reduced enzymatic activity

Summary of Invention Paragraph:
[0119] Other adjuvants include mineral oil and water emulsions, aluminum salts (alum), such as aluminum hydroxide, aluminum phosphate, etc., Amphigen, Avridine, L121/squalene, D-lactide-polylactide/glycoside, pluronic polyols, muramyl dipeptide, killed Bordetella, saponins, such as Quil A or Stimulon.TM. QS-21 (Antigenics, Framingham, Mass.), described in U.S. Pat. No. 5,057,540, which is hereby incorporated by reference, and particles generated therefrom such as ISCOMS (immunostimulating complexes), Mycobacterium tuberculosis, bacterial lipopolysaccharides, synthetic polynucleotides such as oligonucleotides containing a CpG motif (U.S. Pat. No. 6,207,646, which is hereby incorporated by reference), cholera toxin (either in a wild-type or mutant form, e.g., wherein the glutamic acid at amino acid position 29 is replaced by another amino acid, preferably a histidine, in accordance with International Patent Publication No. WO 00/18434, incorporated herein by reference), a pertussis toxin (PT), or an E. coli heat-labile toxin (LT), particularly LT-K63, LT-R72, CT-SI09, PT-K9/G129; see, e.g., International Patent Publication Nos. WO 93/13302 and WO 92/19265, incorporated herein by reference. Various cytokines and lymphokines are suitable for use as adjuvants. One such adjuvant is granulocyte-macrophage colony stimulating factor (GM-CSF), which has a nucleotide sequence as described in U.S. Pat. No. 5,078,996, which is hereby incorporated by reference. A plasmid containing GM-CSF cDNA has been transformed into E. coli and has been deposited with the American Type Culture Collection (ATCC), 10801 University Boulevard, Manassas, Va. 20110-2209, under Accession Number 39900. The cytokine Interleukin-12 (IL-12) is another adjuvant that is described in U.S. Pat. No. 5,723,127, which is hereby incorporated by reference. Other cytokines or lymphokines have been shown to have immune modulating activity, including, but not limited to, the interleukins 1-alpha, 1-beta, 2, 4, 5, 6, 7, 8, 10, 13, 14, 15, 16, 17 and 18, the interferons-alpha, beta and gamma, granulocyte colony stimulating factor, and the tumor necrosis factors alpha and beta, and are suitable for use as adjuvants.

L5: Entry 15 of 46 File: PGPB Jun 10, 2004

DOCUMENT-IDENTIFIER: US 20040110181 A1
TITLE: Novel streptococcus pneumoniae open reading frames encoding polypeptide antigens and uses thereof

Summary of Invention Paragraph:
[0243] As defined hereinafter, an "adjuvant" is a substance that serves to enhance the immunogenicity of an "antigen" or the immunogenic compositions comprising a polypeptide antigens having an amino acid sequence chosen from one of SEQ ID NO:216 through SEQ ID NO:430 or SEQ ID NO: 592 through SEQ ID NO: 752. Thus, adjuvants are often given to boost the immune response and are well known to the skilled artisan. Examples of adjuvants contemplated in the present invention include, but are not limited to, aluminum salts (alum) such as aluminum phosphate and aluminum hydroxide, Mycobacterium tuberculosis, Bordetella pertussis, bacterial lipopolysaccharides, aminoalkyl glucosamine phosphate compounds (AGP), or derivatives or analogs thereof, which are available from Corixa (Hamilton, Mont.), and which are described in U.S. Pat. No. 6,113,918; one such AGP is 2-[(R)-3-Tetradecanoyloxytetradecanoylamino]ethyl 2-Deoxy-4-O-phosphono-3-O-[(R)-3-tetradecanoyoxytetradecanoyl]-2-[(R)-3-t- etradecanoyoxytetradecanoylamino]-b-D-glucopyranoside, which is also known as 529 (formerly known as RC529), which is formulated as an aqueous form or as a stable emulsion, MPL.TM. (3-O -deacylated monophosphoryl lipid A) (Corixa) described in U.S. Pat. No. 4,912,094, synthetic polynucleotides such as oligonucleotides containing a CpG motif (U.S. Pat. No. 6,207,646), polypeptides, saponins such as Quil A or STIMULON.TM. QS-21 (Antigenics, Framingham, Mass.), described in U.S. Pat. No. 5,057,540, a pertussis toxin (PT), or an E. coli heat-labile toxin (LT), particularly LT-K63, LT-R72, CT-S109, PT-K9/G129; see, e.g., International Patent Publication Nos. WO 93/13302 and WO 92/19265, cholera toxin (either in a wild-type or mutant form, e.g., wherein the glutamic acid at amino acid position 29 is replaced by another amino acid, preferably a histidine, in accordance with published International Patent Application number WO 00/18434). Various cytokines and lymphokines are suitable for use as adjuvants. One such adjuvant is granulocyte-macrophage colony stimulating factor (GM-CSF), which has a nucleotide sequence as described in U.S. Pat. No. 5,078,996. A plasmid containing GM-CSF cDNA has been transformed into E. coli and has been deposited with the American Type Culture Collection (ATCC), 1081 University Boulevard, Manassas, Va. 20110-2209, under Accession Number 39900. The cytokine Interleukin-12(IL-12) is another adjuvant which is described in U.S. Pat. No. 5,723,127. Other cytokines or lymphokines have been shown to have immune modulating activity, including, but not limited to, the interleukins 1-alpha, 1-beta, 2, 4, 5,6, 7, 8, 10, 13, 14, 15, 16, 17 and 18, the interferons-alpha, beta and gamma, granulocyte colony stimulating factor, and the tumor necrosis factors alpha and beta, and are suitable for use as adjuvants.

Detail Description Paragraph:
[0352] Six-week old, pathogen-free, male CBA/CaHN xid/j (CBA/N) mice are purchased from Jackson Laboratories (Bar Harbor, Me.) and housed in cages under standard temperature, humidity, and lighting conditions. CBA/N mice, at 10 animals per group, are immunized with an appropriate amount of the protein(s) to be tested. For parenteral immunization, the protein is mixed with 100 .mu.g of MPL.TM. per dose to a final volume of 200 .mu.l in saline and then injected subcutaneously (SC) into mice. All groups receive a booster with the same dose and by the same route 3 and 5

weeks after the primary immunization. Control mice are injected with MPL.TM. alone. All mice are bled two weeks after the last boosting; sera is then isolated and stored at -20.degree. C. For intranasal (IN) immunization, mice receive three IN immunizations, one week apart. On each occasion, an appropriate dose of the protein to be tested is formulated with 0.1 .mu.g of CT-E29H, a genetically modified cholera toxin that is reduced in enzymatic activity and toxicity (Tebbey et al., 2000), and slowly instilled into the nostril of each mouse in a 10 .mu.l volume. Mice immunized with CT-E29H alone are used as controls. Serum samples are collected one week after the last immunization.

Detail Description Paragraph:
[0545] Tebbey et al., "Effective mucosal immunization against respiratory syncytial virus using a genetically detoxified cholera holotoxin, CT-E29H," Vaccine 18 (24):2723-34, 2000.

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